MICROBEAD COMPOSITIONS AND METHODS FOR DELIVERING AN AGENT

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application Ser. No. 62/401,751 filed Sep. 29, 2016, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Traumatic injuries are devastating and their infections can be difficult to treat, often resulting in multiple surgeries and increased costs. Infections can result in high healthcare costs, high mortality rates, and significantly higher amputation rates than those from bacterial infections alone. A limitation of current local therapeutic agent delivery systems is that release is poorly controlled, often resulting in burst release of large amounts of drug followed by sub-therapeutic levels afterward. After releasing drugs, many local delivery systems must then be retrieved, which requires invasive surgical procedures.

[0003] Because current methods for treating or preventing infection are inadequate, improved compositions and methods for providing agents to prevent or treat an infection at a site of trauma are urgently required.

SUMMARY OF THE INVENTION

[0004] As described below, the present invention features compositions comprising chitosan microbeads that provide for the delivery of therapeutic agents, which can be triggered non-invasively for improved control over drug availability.

[0005] In one aspect, the invention provides a microbead containing cross-linked chitosan, a magnetic nanoparticle, and an agent.

[0006] In another aspect, the invention provides a method for producing a chitosan microbead, the method involving dissolving chitosan in an acidic solution; adding magnetic nanoparticles and an agent to the solution; providing a mixture of surfactant, oil, and a polymer; and adding the chitosan solution to the oil and incubating until beads form. In one embodiment, the method further involves incorporating an effective amount of one or more agents into the solution.

[0007] In another aspect, the invention provides a microbead generated according to the method of a previous aspect.

[0008] In another aspect, the invention provides a method for treating or preventing an infection in a subject at a site of trauma, the method involving contacting the site with a chitosan microbead of any previous aspect and applying an external stimulus. In one embodiment, the trauma is selected from a fracture, open fracture, wound, complex wound, or surgical site.

[0009] In another aspect, the invention provides a method for the local and temporally controlled delivery of an agent to a site, the method involving contacting the site with a chitosan microbead containing an agent and applying an external stimulus at a desired time point, thereby temporally controlling delivery of the agent to the site.

[0010] In another aspect, the invention provides a kit containing a chitosan microbead of any previous aspect for use in treating a trauma site or delivering an agent.

[0011] In various embodiments of any of the above aspects or any other aspect of the invention delineated herein, the chitosan is cross-linked to a polymer. In various embodiments of any of the above aspects, the polymer is polyethylene dimethacrylate (PEGDMA) In various embodiments of any of the above aspects, the microbead contains an effective amount of an agent that is any one or more of a polypeptide, polynucleotide or small compound. In various embodiments of any of the above aspects, the agent is an analgesic, angiogenic agent, antimicrobial, antibody, antifungal, anti-inflammatory, anti-thrombotic, chemotherapeutic, growth factor, hormone, or steroid agent. In various embodiments of any of the above aspects, the antimicrobial agent is selected from the group consisting of antifungal, antibacterial, and antiviral agents. In various embodiments of any of the above aspects, the antimicrobial agents are amphotericin B, vancomycin, and/or amikacin. In various embodiments of any of the above aspects, the effective amount of the agent is sufficient to reduce the survival or proliferation of a fungal cell (e.g., *Candida albicans*) or bacterial cell (*Pseudomonas aeruginosa* (lux) or *Staphylococcus aureus*). In various embodiments of any of the above aspects, the composition releases at least about 0.2-50 μg of an antimicrobial agent per hour. In various embodiments of any of the above aspects, the microbead is biodegradable over at least about one, two, three, four, or five days, or one, two, three, or four weeks. In various embodiments of any of the above aspects, the agent is any one or more of an analgesic, angiogenic agent, antimicrobial, antibody, antifungal, anti-inflammatory, anti-thrombotic, chemotherapeutic, growth factor, hormone, or steroid agent. In various embodiments of any of the above aspects, the microbead releases about 2 μg-1000 mg of the agent in 1-72 hours. In various embodiments of any of the above aspects, the stimulus is a magnetic field. In various embodiments of any of the above aspects, the stimulus is a electric field. In various embodiments of any of the above aspects, the stimulus is applied for 30 minutes.

[0012] The invention provides chitosan microbeads comprising a therapeutic agent and methods of using such microbeads for the local delivery of biologically active agents (e.g., antimicrobials, chemotherapeutics) to an open fracture, complex wound or other site of infection or disease. Compositions and articles defined by the invention were isolated or otherwise manufactured in connection with the examples provided below. Other features and advantages of the invention will be apparent from the detailed description, and from the claims.

Definitions

[0013] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise.